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Benjamin Sieniewicz ORCID iD: 0000-0002-9655-7465

Thomas Jackson ORCID iD: 0000-0001-6749-9959

Simon Claridge ORCID iD: 0000-0003-1430-8244

Helder Pereira ORCID iD: 0000-0001-9377-5662

Variation in activation time during bipolar vs extended bipolar left ventricular pacing

Short Title:

ECGI of bipole vs extended bipole

Benjamin J. Sieniewicz MBChB[1, 2], Tom Jackson MBBS[1, 2], Simon Claridge LLB MBBS [1, 2], Helder Pereira MSc[1] , Justin Gould MBBS[1,2], Baldeep Sidhu BS[1, 2], Bradley Porter MBChB[1, 2], Steve Niederer PhD[1], Cheng Yao PhD [3], Christopher A. Rinaldi MD[1,2]

[1] Division of Imaging Sciences and Biomedical Engineering, King's College London, SE1 7EH, United Kingdom

[2] Cardiology Department, Guys and St Thomas' NHS Foundation Trust, London, SE1 7EH, United Kingdom

[3] CardioInsight Technologies, Medtronic, Minneapolis, USA

Corresponding author;

Dr Benjamin J Sieniewicz MBChB MRCP FHEA

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Department of Imaging Sciences and Biomedical Engineering

4th Floor, North Wing, St Thomas' Hospital, London, SE1 7EH, U.K

Tel: +0207 188 9275

Email: benjamin.sieniewicz@kcl.ac.uk

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ABSTRACT

BACKGROUND: Cardiac resynchronization therapy (CRT) is typically delivered via quadripolar leads that allow stimulation using either true bipolar pacing, where stimulation occurs between two electrodes (BP) on the quadripolar lead or extended bipole (EBP) LV pacing, with the quadripolar electrodes and RV coil acting as the cathode and anode, respectively. True bipolar pacing is associated with reductions in mortality and it has been postulated that these differences are the result of enhanced electrical activation.

METHODS: Patients undergoing a CRT underwent an electrocardiographic imaging (ECGI) study where electrical activation data was recorded while different LV pacing vectors were temporarily programmed.

RESULTS: There were no differences in the total electrical activation times or dispersion of electrical activation between biventricular pacing with bipolar or corresponding EBP LV vector configurations (LVtat BP 74.70 ± 18.07 vs EBP 72.4 ± 22.64; P=0.45.) When dichotomized according to aetiology, no difference was observed in the activation time with either BP or EBP pacing (LVtat BP ICM 72.2 ± 17.4 vs BP DCM 79.9 ± 18.9; P=0.38.).

CONCLUSIONS: Bipolar pacing alters the mechanical activation sequence of the LV and is associated with reductions in all-cause mortality. It has been postulated these benefits derive from improvements in electromechanical activation of the LV. Our study would suggest that true bipolar pacing does not necessarily result in more favorable activation of the LV or improved electrical resynchronization and other mechanisms should be explored.

KEYWORDS:

Cardiac Resynchronization Therapy

Multi-polar Pacing

Non-Responders

Bipolar Pacing

Extended Bipolar Pacing

BACKGROUND

Cardiac resynchronization therapy (CRT) is typically delivered via quadripolar leads that allow stimulation via multiple pacing vectors [1]. Selective LV stimulation by the different poles of a quadripolar lead may improve resynchronization by avoiding areas of scar or phrenic nerve stimulation (PNS) with associated improvements in morbidity and mortality [2,3] and demonstrates economic benefits over bipolar leads [4].

Quadripolar leads allow patient specific vector programming and the optimal pacing vector is dependent on multiple factors. Stimulation with quadripolar leads can be performed using true bipolar vectors where stimulation occurs between two electrodes (BP) on the quadripolar lead, see Figure 1. Alternatively extended bipole (EBP) LV pacing is also possible, with the quadripolar electrodes and RV coil or ring acting as the cathode and anode, respectively. When compared with BP pacing, the use of EBP pacing was negatively correlated with CRT response and was found to adversely impact mechanical activation, as determined using echocardiographically derived strain metrics [5]. Furthermore, the use of EBP pacing vectors were associated with adverse outcomes in the MADIT-CRT population, where true bipolar pacing in patients with left bundle branch block was associated with a 54% lower risk of death ($p=0.02$) and a 32% lower risk of combined heart failure admission or death ($p=0.048$) [6].

The exact mechanism underpinning why true bipolar pacing appears more effective than EBP is unclear. One hypothesis is that true bipolar pacing results in a more synchronous activation pattern than EBP and hence better outcomes; however, no detailed activation mapping has previously been performed aimed at comparing BP and EBP vectors. Electrocardiographic imaging (ECGI) is a novel, non-invasive mapping technique capable of detecting detailed patient-specific electrical activation information, allowing the measurement of LV and right ventricular (RV) activation times [7,8].

We hypothesized that BP and EBP programming would have divergent effects on measures of LV activation. We set out to study the effects of BP and EBP pacing vectors from a quadripolar lead by evaluating ECGI measures of ventricular activation and dispersion in CRT patients using body surface mapping.

METHODS

The study conformed to the principles of the Declaration of Helsinki on research in human subjects and all subjects gave written informed consent (approved by the Research Ethics Committee, ClinicalTrials.gov Identifier: NCT01831518.) Patients on optimal medical therapy (OMT) meeting European Society of Cardiology (ESC)[9] and/or Heart Rhythm Society (HRS)[10] criteria for CRT were enrolled in the study. The underlying aetiology of heart failure was determined using angiography, clinical history, or cardiac MRI (CMR)

Pacemaker implant

CRT implantation was performed with the RV lead positioned at the RV apex or high RV septum. The right atrial lead was placed in the right atrial appendage. All LV pacing leads were Abbott Quartet leads™ positioned in the lateral or postero-lateral vein of the coronary sinus, aiming for all four poles of the quadripolar lead to be within the vein to allow for stimulation from all the poles. If this was not possible, an alternative location was chosen in the anterolateral, posterior, or anterior locations.

CRT Configuration Optimization

Twenty-four hours post CRT implant, patients underwent a temporary biventricular endocardial pacing study accompanied by body surface mapping (BSM). Iterative echo guided optimization of atrioventricular delay (AVD) and LV and RV (VV) delay was first performed to establish the optimal AVD and VV delay for each patient, as previously described [11,12]. Subsequently, all the available BP and EBP pacing vectors were programmed and tested.

ECGI was performed using a CardioInsight ecSYNC system (CardioInsight Technologies Inc., Cleveland, OH). Non-invasive biventricular epicardial electrograms were analyzed to construct 3D isochrone and isopotential activation maps, as previously described [13]. Ventricular activation times were calculated from the onset of the QRS to the maximal negative slope of each electrogram and combined to construct 3D epicardial isochrone maps. After the acquisition of vest electrograms, subjects underwent a thoracic computed tomographic (CT) scan with the vest still in position, to determine the precise anatomic relation between the cardiac geometry and the torso electrodes. This process allows the reconstruction 1500 unipolar electrograms on the epicardial surface of the heart. ECGI maps were created on a beat-by-beat basis for all available quadripolar LV lead configurations in a DDD pacing mode. The use of ECGI mapping meant it was possible to confirm the presence of true biventricular electrical capture and exclude anodal capture during each programmed pacing configuration.

Multiple electrocardiographic measurements were recorded including total ventricular total activation (VVtat), the difference between LV and RV activation (VVsync), left ventricular total activation time (LVtat) & dispersion of left ventricular activation times (LVdisp). These measures have previously been validated in the assessment of patients undergoing ECGI during CRT [14–18].

Statistical analyses

Statistical analyses were performed using PASW Statistics 21 (SPSS Inc., Chicago, IL). Data was tested for normality with the Shapiro-Wilk test. Significance testing on normally distributed paired data was performed using two tailed paired *t* tests. Significance testing on non-normally distributed paired data was performed using the Wilcoxon Signed Rank test. Significance testing on non-normally distributed un-paired data was performed using the Mann-Whitney U test. Results were considered significant at $p < 0.05$.

RESULTS

A total of 18 patients were recruited and underwent a temporary pacing and electroanatomical mapping study. Mean patient demographics for our cohort are shown in Table 1, while individual patient data is shown in Table 2. Patients were predominantly male (78%) with a mean age of 68.6 ± 12.8 years, the mean LVEF was 25.6% ± 7.4%. The mean baseline QRS duration was 164.4 ± 19.3ms. There was a near equal distribution between ischemic (n=10) and non-ischemic (n=8) etiology.

Bipolar CRT vs Extended Bipolar CRT

Each patient underwent temporary programming in order to analyze EBP with BP CRT. Analysis of the body surface maps excluded anodal capture and confirmed true biventricular capture with EBP in all patients. A total of 97 different pacing configurations were assessed in our cohort (57 BP and 40 EBP, mean 5.3 configurations per patient). On average, each patient received CRT pacing with a combination of three BP configurations and two EBP configurations. ECGI mapping appeared to show a significant difference in the degree of electrical resynchronization when alternating between BP and EBP pacing, Figure 2; however, no statistically significant differences in activation were observed between BP and EBP vectors for the whole group. There was also no statistically significant difference between activation metrics between EBP and BP CRT, Figure 3.

Etiology vs Electrical Activation

The presence of ischemic heart failure etiology is known to adversely impact outcome [19].

Intuitively among patients with ischemic scar, bipolar LV pacing should be capable of achieving a superior degree of electrical resynchronization than extended bipolar pacing by allowing the bypassing of scarred areas of myocardial tissue. Both modelling [20] and hemodynamic data [21] support the hypothesis that the multiple wave fronts arising from areas of simultaneous bipolar stimulation improve response among patients with ischemic scar. Our cohort was dichotomized on the basis of ischemic and non-ischemic etiology, in order to ascertain whether the hemodynamic benefits associated with BP pacing were a result of more rapid electrical activation.

Again, no significant difference in any ECGI measure was observed during BP and EBP pacing, Figure 4.

DISCUSSION

We assessed the effect of utilizing BP and EBP vectors on non-invasive electrocardiographic markers of ventricular activation in patients receiving CRT with a quadripolar lead. The demonstration of true biventricular capture with body surface mapping excluded the possibility that anodal stimulation had a significant effect on the measured activation parameters.

The main findings of the current study were that:

1) There were no differences in the total electrical activation times or dispersion of electrical activation between biventricular pacing with bipolar or corresponding EBP LV vector configurations.

2) When dichotomized according to etiology, no difference was observed in the activation time with either BP or EBP pacing.

Comparison with previous studies

Prior studies have shown that alterations in LV electrical activation between BP and EBP are associated with different mechanical activation patterns. Yang et al studied the relationship between polarity of left ventricular (LV) pacing and the resultant regional, global, and transmural mechanical sequence of contraction in 20 patients with preexisting biventricular devices [5]. Regional and global LV longitudinal and radial mechanics were assessed with 2D speckle-tracking echocardiography. The authors found that unipolar pacing resulted in increased dispersion of LV regional endocardial strain with a difference in the mechanical activation sequence of the LV between unipolar vs. bipolar pacing stimulation.

Furthermore, Jame et al retrospectively analyzed 969 patients with CRT-D implants from the MADIT CRT study and demonstrated that in patients with LBBB undergoing CRT, true bipolar LV lead pacing had a significantly lower risk of all-cause mortality and heart failure death compared with extended unipolar/extended Bipolar LV pacing [6]. These findings were consistent in patients across both ischemic and non-ischemic etiologies and independent of LV lead location. The authors suggested that in the absence of other contraindications, true bipolar LV pacing may be preferable to unipolar or extended bipolar vectors. Although there were significant reductions in mortality (54% lower risk) and heart failure/death, true bipolar pacing did not increase LV remodelling or improve LV dyssynchrony one year after CRT. Despite this, the authors postulated that the improved outcome conferred by true bipolar pacing may be the result of differences in electromechanical activation of the left ventricle. Our findings would refute this and instead would suggest that true bipolar pacing does not necessarily result in more favorable activation of the LV or improved resynchronization . Instead, individual patients may experience benefit from a particular pacing strategy and individual customization of the pacing vector may be required to achieve optimal resynchronization.

Clinical importance

Quadripolar LV leads represent the standard of care for the delivery of CRT. The presence of additional poles means it is possible to program stimulation around areas of scar and avoid PNS. Optimizing pacing vector configuration has been shown to be associated with improvements in outcome. Our findings suggest that extended bipolar vectors are not inferior to true bipolar vectors in terms of ventricular activation indices assessed with ECGI. Although optimization may need to be tailored to the individual patient, our results would suggest that while extended bipolar vectors are associated with higher battery usage they appear to represent a viable alternative to true bipolar vectors in terms of electrical resynchronization.

Limitations

The main limitation of the current study is the lack of correlation between body surface mapping and the surface ECG. Although surface ECG's were analyzed at baseline during the temporary acute pacing study, it was not possible to undertake simultaneous standard 12- lead ECG analysis, due to the presence of the CARDIOINSIGHT mapping vests composed of over 250 electrodes, which covered both the front and back of the thorax. We agree that it would be important to investigate how the 12-lead surface ECG changes during EBP vs BP pacing, but this is not performed as this study was specifically designed to investigate the hypothesis that EBP would be associated with inferior electrical resynchronization than BP, and as such the use of the ECGI vests was essential to the testing of our hypothesis.

This is a small study and the results are hypothesis generating rather than conclusive. The non-invasive electrical measurements were performed acutely and it is unclear whether these results can be extrapolated to the chronic delivery of CRT. Some of the vectors tested resulted in PNS, which would limit their use to deliver

CRT effectively. We did not specifically assess the presence of myocardial scar and/or lead position in relation to electrical activation. Improvements in electrical resynchronization were not validated against hemodynamic change in this study, although a dependant relationship between these two indices has previously been described [22].

CONCLUSION

No significant difference was observed in any metric of electrical activation during biventricular pacing with bipolar or corresponding EBP LV vector configurations. These results suggest that the reported outcome benefits associated with bipolar LV pacing are not the result of improved activation. More work is needed to understand why true bipolar pacing may be beneficial in left bundle branch block patients.

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FIGURES

Figure 1. Schematic representation of Quadripolar vectors tested. True bipolar vectors between the poles of the Quartet ™ LV lead are demonstrated on the right of the image. Extended bipolar (EBP) vectors incorporate the RV pacing lead.

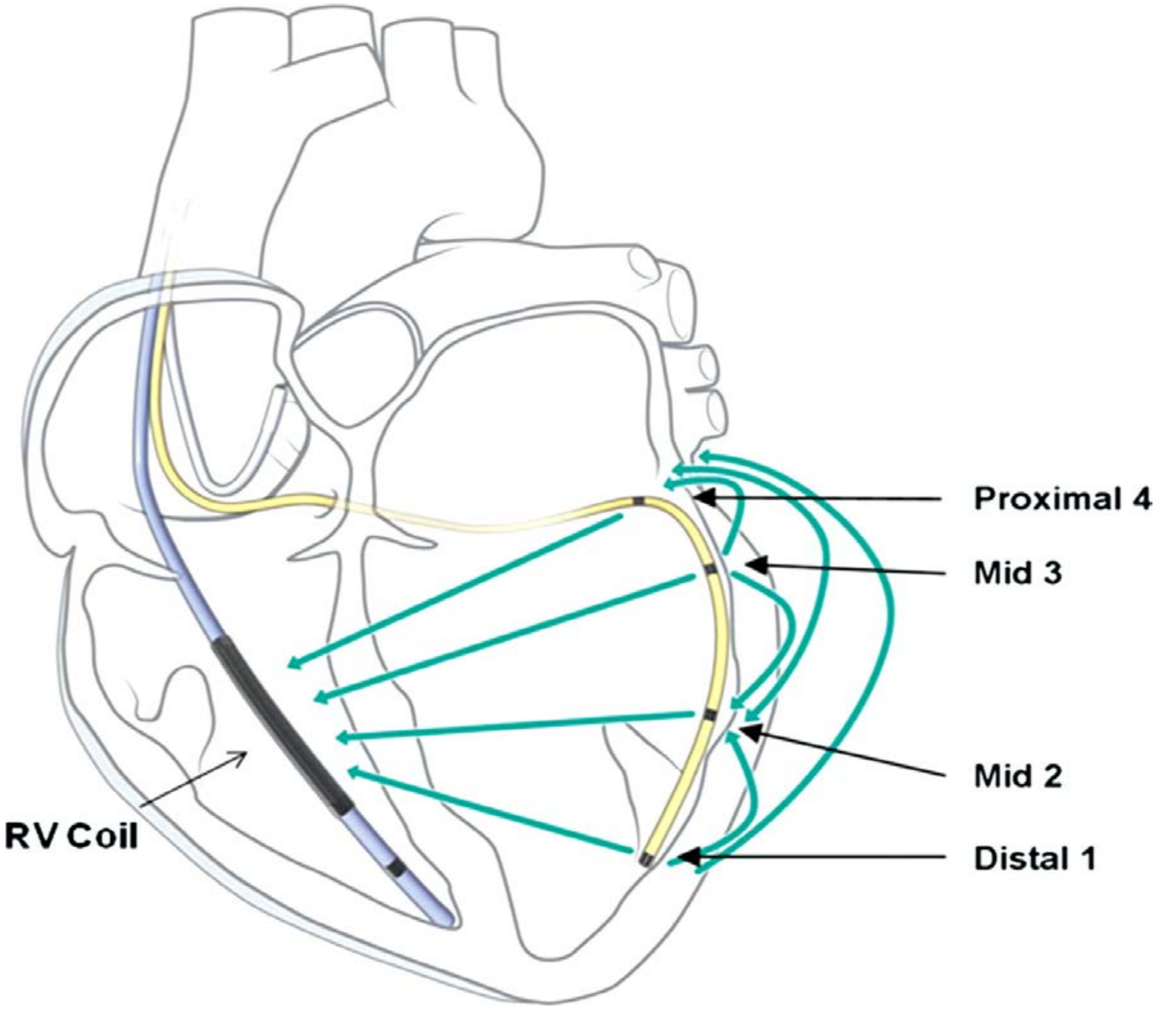


Figure 2. Variance in the degree of electrical resynchronization achieved during different EBP and BP pacing configurations. Left lateral views of body surface directional activation maps of biventricular pacing through 4 quadripolar extended bipolar vectors (on the left) and 4 bipolar pacing vectors (on the right). Red areas represent early activation, while blue represent late activation. The dotted yellow line represents course of left anterior descending artery. Grey dots outside cardiac silhouette represent the location of quadripolar pacing cathodes.

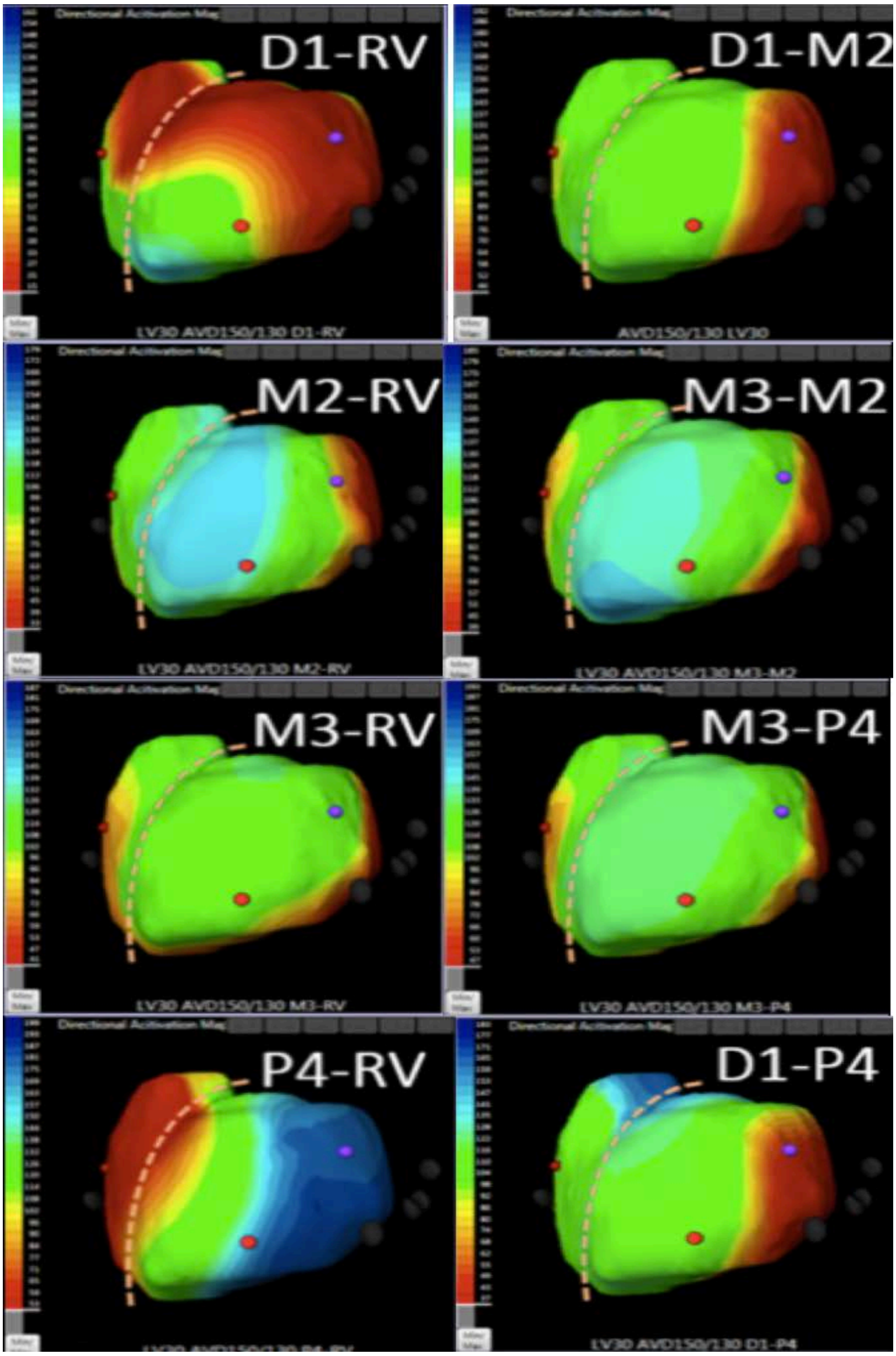


Figure 3. Box and whisker plots of total ventricular total activation (VVtat), the difference between LV and RV activation (VVsync), left ventricular total activation time (LVtat) & dispersion of left ventricular activation times (LVdisp) for true bipolar and extended bipolar biventricular pacing.

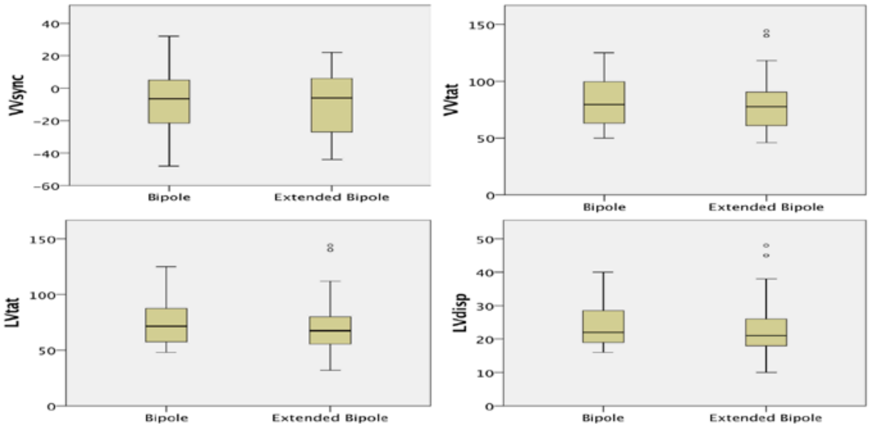
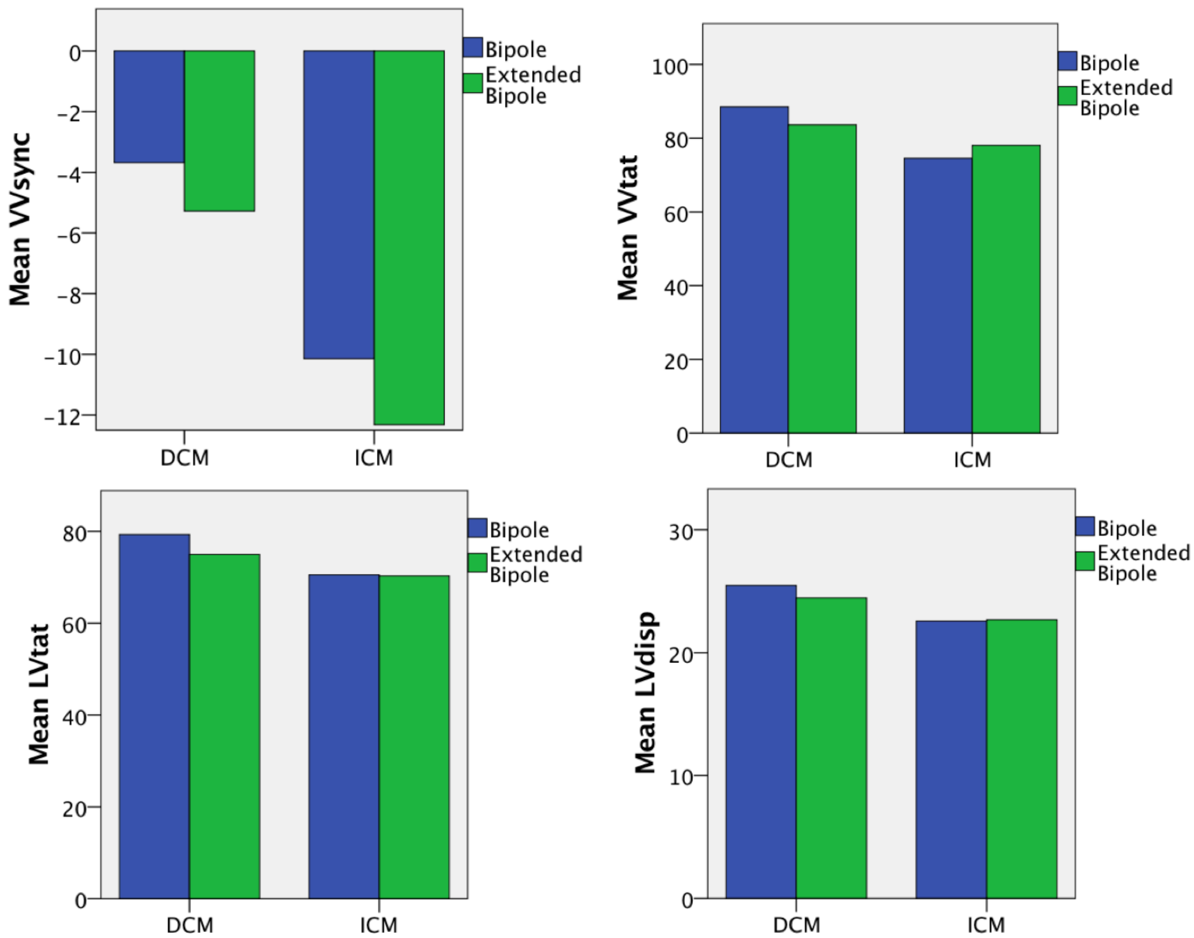


Figure 4. Bar graphs displaying the impact of aetiology in BP vs EBP electrical activation.



TABLES

TABLE 1. Patient Demographics

	Mean ±SD or Numbers (%)
Patients	18
Age (years)	68.6± 12.8
Male (%)	14 (77.8%)
LVEF (%)	25.6% ± 7.4
NYHA	2.9 ± 0.4
QRS duration (ms)	164.4 ± 19.3
QRS Morpholgy	
LBBB	12 (66.7%)
RV Paced	5 (27.8%)
RBBB	1 (5.6%)
Etiology	
ICM (%)	10 (55.6%)

TABLE 2: Individual patient demographic data

Age	Gender	Aetiology	NYHA Pre	Rhythm	Baseline QRS Morph	QRS duration	LVEF%
67	M	ICM	3	NSR	LBBB	184	29
72	M	DCM	3	NSR	RV paced	182	9
82	M	DCM	2	NSR	LBBB	158	33
49	F	DCM	3	NSR	LBBB	200	31
87	M	DCM	3	AF	RV paced	180	25
62	M	ICM	3	NSR	LBBB	134	20
87	M	ICM	3	NSR	LBBB	168	30
77	M	ICM	3	NSR	LBBB	162	22.5
69	F	DCM	2	NSR	RV paced	166	22
49	M	DCM	3	AF	LBBB	130	25
62	F	DCM	3	NSR	LBBB	144	29
59	M	ICM	3	NSR	LBBB	160	30
82	F	DCM	3	AF	RV paced	174	34
76	M	ICM	3	NSR	RBBB	174	17
55	M	ICM	3	AF	LBBB	174	12.5

49	M	DCM	4	NSR	LBBB	177	32.5
78	M	ICM	3	AF	RV paced	160	35
73	M	ICM	3	NSR	LBBB	132	25